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| ART UNIT | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/031,640 | PRAKASH ET AL. | |
| | Examiner | Art Unit | |
| | Robert M Kelly | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-16 are currently pending.

### *Election/Restrictions*

Applicant's election without traverse of Group I, Claims 1-13, and the species alginate-polylysine-alginate of Claims 4 and 13 in the reply filed on 17 May 2004 is acknowledged.

Claims 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 17 May 2004.

Claims 1-13 are presently considered with respect to the elected species, alginate-polylysine-alginate.

### *Double Patenting*

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-9, and 11-13 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-9 of prior U.S. Patent No. 6,217,859. This is a double patenting rejection.

Claims 1-5 encompass a composition for the removal of at least one undesired electrolyte and/or metabolite, such composition comprising metabolically induced *E. coli* cells, which cells

have been genetically engineered to be capable of removing the undesired electrolyte and/or metabolite and are further microencapsulated in artificial cells (alginate-polylysine-alginate), and wherein such electrolyte is chosen from the group consisting of K, Mg, Na, Cl, and wherein such metabolite is chosen from the group consisting of uric acid, cholesterol, bilirubin, and creatinine, and wherein such removal of the electrolyte and/or metabolite lowers the concentration of the undesired electrolyte(s) and/or metabolite(s) to a therapeutically acceptable level. Claim 2 limits the cells to be encapsulated in any material that retains the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter the microcapsules. Claim 3 limits the cells to being entrapped within any material that can retain the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter and contact the cells. Claim 4 limits the microencapsulation material to, *inter alia*, alginate-polylysine-alginate. Claim 5 limits the metabolic induction of the DH5 cells to fermentation induction.

Claims 6-9 and 11-13 of the instant Application encompass a method of treatment of any disease with elevated levels of any undesired electrolytes and/or any undesired metabolites in the body of any patient, comprising treating the patient with any composition for the removal of at least one undesired electrolyte and/or metabolite, wherein the composition comprises *E. coli* DH5 cells, genetically engineered to be capable of removing the undesired electolyte(s) and/or metabolite(s), wherein said cells are microencapsulated in artificial cells (alginate-polylysine-alginate). Claims 7-9 limit the disease to any kidney-failure causing, any liver-failure causing, and any hyperammonemia with elevated ammonia levels, disease. Claims 11 and 12 limit the DH5 cells to being either microencapsulated in a material that allows the undesired electrolytes/metabolites to enter, or entrapped in entrapment material that allows the

electrolytes/metabolites to contact the cells. Claim 13 limits the microencapsulation material to, *inter alia*, alginate-polylysine-alginate.

Claims 1-9 of prior U.S. Patent No. 6,217,859 encompass a method of reducing the concentration of ammonia and/or urea in a mammal, comprising the oral administration of DH5 cells engineered to express *K. aerogens* urease gene, said cells encapsulated in alginate-polylysine-alginate, and further comprising a carrier. Claim 2 limits the cells to be encapsulated in any material that retains the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter the microcapsules. Claim 3 limits the cells to being entrapped within any material that can retain the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter and contact the cells. Claim 4 requires the ammonia levels and/or urea levels to be caused by a disease. Claims 5-7 limit the disease to any kidney-failure causing, any liver-failure causing, and any hyperammonemia with elevated ammonia levels, disease. Claim 8 limits the encapsulation material to the same materials as Claims 4 and 13 of the instant application. Claim 9 is drawn to the same method as claim 1 for reducing urea concentration in a mammal.

Hence these claims encompass many of the same embodiments, including any disease where urea or ammonia needs to be reduced, the same cells, and encapsulation materials. Moreover, the claims of U.S. Patent No. 6,217,859 require the use of materials within the scope of claims 1-5 of the instant applicant, because these materials would be required to practice the invention claimed in U.S. Patent No. 6,217,859.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, 9, and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "metabolically induced genetically engineered E. coli DH5 cells microencapsulated in artificial cells to be capable of removing said undesired electrolyte and/or metabolite". The metes and bounds of this limitation are unclear.

Claims 2-3 and 11-12 each recite the limitation "can retain the [E. coli DH5] cells". The metes and bounds of this limitation are unclear.

Claim 3 recites the limitation "DH5 cells are entrapped within a carrier using any entrapment material". The metes and bounds of this limitation are unclear.

Claim 3 further recites the limitation "to enter in contact". The metes and bounds of this limitation are unclear.

Claim 6 recites the limitation "genetically engineered E. coli DH5 cells microencapsulated in artificial cells to be capable of removing said undesired electrolyte and/or metabolite". The metes and bounds of this term are unclear.

Claim 6 further recites the limitation "to enter in contact". The metes and bounds of this limitation are unclear.

Claim 6 is further rejected under 35 USC 112, second paragraph, for failing to recite a positive step of treatment.

Claim 9 is recites the limitation "hyperammonemia with elevated ammonia levels". The metes and bounds of this limitation are unclear.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claims 1 and 6 encompasses E. coli DH5 cells, genetically engineered to be capable of removing at least one electrolyte and/or metabolite. Within Claim 1, the electrolytes are limited to K, Mg, P, Na, Cl, and the metabolites are limited to uric acid, cholesterol, bilirubin, and creatinine.

These agents of these claims are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses that the DH5 cells are genetically engineered for lowering of K, Mg, P, Na, Cl, uric acid, cholesterol, bilirubin, and creatinine in a patient (p. 6, lines 1-10).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only one single example of a genetically engineered DH5 cell is given: DH5 cells transformed with the urease gene from Klebsiella aerogens (p. 6, lines 28-32). However, such single disclosure does not provide the requisite structure to allow the

artisan to determine the different species that would be used to genetically engineer DH5 cells to remove any electrolyte, or any other metabolite, except uric acid. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristic is that the DH5 cells, after being genetically engineered can remove the selected metabolite(s) and/or electrolyte(s) (p. 6, lines 1-10).

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any genetically E. coli DH5 cell capable of lowering any metabolite and/or any electrolyte in a patient, at the time the application was

filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) a composition for the removal of uric acid in a rat comprising:

E. coli DH5 cells, genetically engineered to express the *Klebsiella aerogens* urease gene, and microencapsulated in alginate-polylysine-alginate,

wherein upon oral administration of the composition, endogenous uric acid reacts with the expressed urease protein to produce ammonia, carbon dioxide, and water, thereby lowering the level of uric acid; and

(ii) a method for the treatment of a disease in a rat characterized by elevated levels of uric acid, the method comprising:

oral administration of a composition of E. coli DH5 cells, genetically engineered to express the *Klebsiella aerogens* urease gene, which cells are microencapsulated in alginate-polylysine-alginate,

wherein upon oral administration of the composition, the rat's endogenous urea reacts with the expressed urease protein to produce ammonia, carbon dioxide, and water, thereby lowering the level of uric acid by mass-action in the patient and effecting treatment,

the specification does not reasonably provide enablement for *E. coli* DH5 cells genetically engineered to remove any metabolite and/or any electrolyte, the use of any genetically engineered *E. coli* DH5 cells, *E. coli* DH5 cells that are not genetically engineered for the removal of the specific metabolite which is to be removed, the treatment of any disease, or the treatment of any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its

full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

**The Breadth of the Claims**

Claims 1-13 are broad in scope (Applicant is reminded that the Claims are only examined with regard to the elected species: alginate-polylysine-alginate.) The following paragraphs outline the full breadth of the claims.

Claims 1-5 encompass a composition for the removal of at least one undesired electrolyte and/or metabolite, such composition comprising metabolically induced *E. coli* cells, which cells have been genetically engineered to be capable of removing the undesired electrolyte and/or metabolite and are further microencapsulated in artificial cells (alginate-polylysine-alginate), and wherein such electrolyte is chosen from the group consisting of K, Mg, Na, Cl, and wherein such metabolite is chosen from the group consisting of uric acid, cholesterol, bilirubin, and creatinine, and wherein such removal of the electrolyte and/or metabolite lowers the concentration of the undesired electrolyte(s) and/or metabolite(s) to a therapeutically acceptable level. Claim 2 limits the cells to be encapsulated in any material that retains the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter the microcapsules. Claim 3 limits the cells to being entrapped within any material that can retain the cells, yet allows the electrolyte(s) and/or metabolite(s) to enter and contact the cells. Claim 4 limits the microencapsulation material to, *inter alia*, alginate-polylysine-alginate. Claim 5 limits the metabolic induction of the DH5 cells to fermentation induction.

Claims 6-13 encompass a method of treatment of any disease with elevated levels of any undesired electrolytes and/or any undesired metabolites in the body of any patient, comprising

treating the patient with any composition for the removal of at least one undesired electrolyte and/or metabolite, wherein the composition comprises *E. coli* DH5 cells, genetically engineered to be capable of removing the undesired electolyte(s) and/or metabolite(s), wherein said cells are microencapsulated in artificial cells (alginate-polylysine-alginate). Claims 7-9 limit the disease to any kidney-failure causing, any liver-failure causing, and any hyperammonemia with elevated ammonia levels, disease. Claim 10 limits the electrolytes to any of K, Mg, P, Na, and Cl, and the metabolites to any of uric acid, cholesterol, bilirubin, and creatinine, and that such administration yields therapeutically acceptable levels of such electrolyte(s) and/or metabolite(s). Claims 11 and 12 limit the DH5 cells to being either microencapsulated in a material that allows the undesired electrolytes/metabolites to enter, or entrapped in entrapment material that allows the electrolytes/metabolites to contact the cells. Claim 13 limits the microencapsulation material to, *inter alia*, alginate-polylysine-alginate.

Because the composition claims recite an intended use, such use must be enabled. The use roughly tracks the method claims. Furthermore, such claimed uses and such method claims must be enabled for their full scope (MPEP § 2164.01(a..c), et seq.). However, Applicant's claims are broad in scope, encompassing many metabolites, many genetically engineered DH5 cells, removal by any method, the removal of electrolytes/metabolites for which the DH5 cell has not been engineered to remove, administration of the compositions by any method and the treatment of any disease. In view of such broad scope, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other words, those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art at the time of invention by Applicant

(hereinafter the "Artisan") would be able to practice the invention, and do so to its fully claimed scope, without an undue burden being imposed on such Artisan. Undue burden is generally found because undue experimentation is required by one of skill in the art to produce functioning embodiments of the claimed invention, effectively causing the Artisan to reduce Applicant's invention to practice because Applicant has not done so.

As will be discussed below, Applicant has not met their burden to enable the full scope of these claims.

**The Nature of the Invention**

The invention is in the nature of *E. coli* cells, genetically engineered to remove metabolites and/or electrolytes from an organism, *in vivo*. Such inventions are generally not enabled by the nature of the invention.

The most recent review of the field is a 1999 article, Chang (1999) Ann. NY. Acad. Sci., 875: 71-83, and Mr. Chang is an inventor of this Application. With regard to administration in any route other than oral administration, Chang notes that there exist many problems, including material biocompatibility, foreign body reaction, compliment activation, resulting in problems with long-term retention and survival of cells and mass-transfer of enzymes, electrolytes and metabolites across the microencapsulation barrier (e.g., pp. 75-76). Moreover, the studies reviewed are generally directed toward encapsulated eukaryotic cells, not the claimed prokaryotic cells. Hence, the same problems would be exacerbated, as bacteria are even more distantly related to eukaryotes, causing even larger immune responses than other eukaryotes. Furthermore, even though a number of promising demonstrations of methods of administering such cells had taken place (e.g., pp. 76-78), mostly with eukaryotic cells, these showings are

specific to the species that is being treated, the material used, the type of cell used, and the transgene used, because there is no disclosure that would allow the Artisan to reasonably predict which of each of these aforementioned species, material, cell, and transgene, and method of administration, in combination, would produce a therapeutic effect. Lastly, with regard to these forms of treatment, Chang echoes these sentiments in the statement "A number of problems still need to be resolved before transplantation of microencapsulated genetically engineer[ed] cells can be used clinically. These include the need to inject genetically engineered cells and the retention and biocompatibility of implanted microcapsules." (p. 78, third paragraph).

Hence, with regard to administration of microencapsulated cells, other than by oral administration, compatibility problems between: the cells, the cell's expressed transgene, and the host, precludes the Artisan from being able to reasonably predict that any cell type can be microencapsulated and administered by any method to any patient. The reason for this is that the Artisan would not be able to predict, absent a specific showing, that the route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected.

With regard to oral administration, at the time of this publication, Chang notes that the approach was "promising" (p. 76, first paragraph). Moreover, Chang reviews his own work, which appears to be the vanguard of orally-administered microencapsulated cells to effect treatment (pp. 78-81). Chang's describes experiments in rats, which have undergone surgery to induce renal failure. A portion of these rats were orally administered DH5 cells which were genetically engineered to express the urease gene from *K. aerogens*, microencapsulated in

alginate-polylysine-alginate. Those rats treated with such microencapsulated DH5 cells exhibited a much lower level of urea than rats not treated. In fact the level was similar to that of normal rats (p. 79, first paragraph).

However, outside of this single showing with DH5 cells, the Artisan could not reasonably predict that any disease could be treated, any gene could be used, any genetically modified DH5 cell could be used, or any electrolyte or metabolite could be lowered. Even the removal of uric acid could not be reasonably predicted, because uric acid is a different molecular entity. Although uric acid is related to urea sharing common pathways, leading to urease digestion of urea, uric acid, the cause of gout, crystallizes in the joints and kidneys and other organs not local to the intestine, and such crystals are therefore stabilized. Therefore, it is not reasonably predictable that urease could even cause the lowering of uric acid to acceptable levels even with Chang's showing that urea levels may be reduced because the uric acid would have to dissolve, enter the metabolic pathways that lead to formation of urea, be sent to the intestine, and converted into carbon dioxide, ammonia, and water. Such events are not reasonably predictable to happen to an appreciable extent such that any therapy would be effected.

Also, Chang performed a number of studies to determine if the release of the DH5 cells was damaging to the rats (pp. 79-81, paragraph bridging). Such was important because the release of the DH5 cells could change the natural flora of the intestine, which could cause dysentery, and death, of the animal (Id.). While such tests demonstrated that, in this case, even if all the DH5 cells were to escape microencapsulation, the rats would survive, it further draws attention to the Artisan that the microencapsulation material may break, causing release, and possibly death, of the animal before any treatment could be effected. Also, such released DH5

cells may cause death in other animals before treatment could be effected, as different animals have different flora, which would make the rats used not reasonably predictive of other animals. Still also, the specific metabolites and electrolytes would effect the activity of the patient and the DH5 cells, making the Artisan even less able to predict that any metabolite or electrolyte could be treated with any DH5 cell and any microencapsulation material. Moreover, because the breakage of the material would depend on the molecular structure of the material being used to encapsulate the cells, one material would not be reasonably predictive of another and the same electrolytes and metabolites would also effect the susceptibility to breakage of any particular material. Lastly, Chang did not even demonstrate that the material used did not break, but only that, in the case of rats, even if the material did break, it caused no adverse effects on the rat (Id.).

Hence, with regard to oral administration, the Artisan would not be able to predict anything other than that high uric acid levels in rat, caused by surgically induced renal failure, could be treated with DH5 cells genetically to express *K. aerogens* urease, and microencapsulated in alginate-polylysine-alginate, by the oral administration of such microencapsulated cells. The reason for such a low level of predictability is that any particular microencapsulation material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes, may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected.

**The State of the Prior Art**

The prior art does not offer any more enabling disclosure over that of the Nature of the Invention. Below a few articles and patents are addressed to demonstrate that the Art has not progressed past the points the discussed in the Nature of the Invention.

Applicant's issued patent, U.S. Patent No. 6,217,859, to Chang, et al., filed 20 July 1997, patented 17 April 2001, provides for the use of microencapsulated genetically engineered microorganisms for clinical application. While broad discussion covers a wide range of cells, genes, and metabolites and electrolytes (cols. 1-6), such discussion also notes that "parental administration of microorganism[s] into human is too risky and dangerous, even if a very small amount is given." (col. 1, lines 17-19). Hence, Chang recognizes the unpredictability in the Art in this patent, and such unpredictability, although applied to humans, extends to other animals; in the case of humans, however, we are more careful than with other animals, because the death of a rat is not valued as much as human death. Moreover, the unpredictability is due to the reasons given in the Nature of the Invention – e.g., leakage, specific organism, specific species, etc., (e.g., col. 1, lines 21-27). Lastly, Chang's examples track that disclosure of Chang (1999) Ann. NY. Acad. Sci., demonstrating urea removal by the same cells, and consequent excretion of ammonia, and lowered plasma levels of urea. Hence, change contributes nothing over the Nature of the invention to enable Applicant's claimed invention.

Perhaps the most recent article on the oral administration of genetically-engineered microencapsulated cells is that Jones, et al. (2004) J. Biomed. Biotech., 1: 61-69. Here, Jones (actually part of inventor Prakash's group) reports the use of *Lactobacillus plantarum* 80 cells cells for lowering serum cholesterol (ABSTRACT). However, these cells are not Applicant's

claimed DH5 cells, and these cells have not been genetically engineered. Hence, for the same reasons as given with respect to the nature of the invention, these experiments are not reasonably predictive of any treatment with any DH5 cells and any other microencapsulation material, to remove any particular metabolite(s) and/or electrolyte(s).

Applicant's published articles Prakash, et al. (1999) Art. Cells, Blood Subs., Immob. Biotech., 27(5-6): 475-81, Prakash, et al. (2000) Art. Cells, Blood Subs., Immob. Biotech., 28(5): 397-408, and Prakash, et al. (2000) Int. J. Art. Organs, 23(7): 429-35, present the same data that is provided in Applicant's specification; hence, these articles are not addressed in detail here, but the analysis of the data is left for discussion in the sections on guidance and direction, and working examples, below. Also, important comments provided by Applicant in these articles is discussed in the analysis in the aforementioned sections, which comments support the Examiner's conclusions.

Hence, the state of the prior art contributes nothing over that of the nature of the invention with regard to predictability. Artisan would not be able to predict, absent a specific showing, that the route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected. Moreover, the Artisan could not reasonably predict whether any particular microencapsulation material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes, may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected.

For the reasons given above, absent a strong showing by way of specific guidance and direction and/or examples, the invention is not enabled for its full scope, as claimed by Applicant.

**The Level of One of Ordinary Skill in the Art at the Time of Invention**

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

**The Level of Predictability in the Art**

Because the art, as shown above, does not disclose sufficient information for the Artisan to reasonably predict, absent a specific showing, that the route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected or to reasonably predict whether any particular microencapsulation material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes, may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

**The Amount of Direction and Guidance Provided By Applicant**

The specification broadly discusses Applicant's claimed electrolytes and metabolites, their relations to disease, and the need for a method to lower these electrolytes and metabolites (pp. 1-2). This is followed by a summary roughly tracking the claim language (pp. 2-4). The detailed description, beginning on page 6, discusses broadly the metabolites and electrolytes claimed, the usefulness of the invention, the microencapsulation materials, DH5 cells expressing urease, induction procedures, microencapsulation procedures, storage procedures, plasma descriptions, *in vitro* experimental procedures, surgical procedures, *in vivo* experimental procedures, description of lowering *in vitro* potassium levels, phosphorus levels, magnesium levels, sodium levels, chloride levels, cholesterol levels, bilirubin levels, creatinine levels, and uric acid levels (pp. 6-17). However, it is worth noting that these descriptions were carried *in vitro*, where such problems as discussed above in the nature of the invention, and repeated throughout, are of no consequence. Moreover, the DH5 cells were only genetically engineered to digest urea, not to lower any other electrolyte or metabolite levels. Lastly, the depletion of these electrolytes and metabolites is easily explained on the basis of cell metabolism: these cells are growing *in vitro* and therefore depleting the materials present. However, this would not make any *in vivo* use enabled, because animals have a constant influx of food and therefore make more metabolites and have an influx of electrolytes that would have to be overcome. Therefore,

the Artisan would not find simple depletion of an existing pool of metabolites *in vitro* reasonably predictive of the *in vivo* conditions claimed.

Moreover, Applicant's disclosure points out another level of unpredictability in the Art. Applicant is using the urease gene. Applicant, however, has not disclosed any other gene which may be used to genetically engineer DH5 cells to remove any other metabolite or any electrolyte. Furthermore, in view of the non-enabling nature of the invention, the Artisan would not be able to reasonably predict which gene to use in a DH5 cell to remove any particular metabolite, except that urease genes may be used to remove urea.

These questions left to be addressed by the Artisan due to the unpredictability of particular issues are echoed by certain sentiments made by the Applicant in their non-patent publications. For example, Prakash, et al. (1999) Art. Cells, Blood Subs., Immob. Biotech., 27(5-6): 475-81, which provides a preliminary report on the use of these microencapsulated DH5 cells for lowering K, Mg, P, Na, Cl, uric acid, cholesterol, and creatinine *in vitro* (ABSTRACT). Moreover, the results roughly track that data of Applicant's disclosure (Article in general). In this report, the Applicant has stated "These preliminary results encourage further *in vivo* studies to study the feasibility of removal of one or more of these metabolites from the body for a number of potential applications." (pp. 479-80, paragraph bridging). Moreover, this article only provides the same genetically engineered DH5 cell discussed throughout (p. 476, paragraph 5). From this, the Artisan would recognize that these results are simply an invitation for further experimentation, because the Artisan could not reasonably predict from *in vitro* results whether an *in vivo* therapeutic effect would occur and the Artisan could not reasonably predict how to

genetically modify any DH5 cell to produce any particular efficacious effect. Such prediction is precluded for the reasons given throughout this analysis.

In Prakash, et al. (2000) Art. Cells, Blood Subs., Immob. Biotech., 28(5): 397-408, results are given for the lowering of plasma creatinine *in vivo* and *in vitro* by such microencapsulated DH5 cells (ABSTRACT). However, such *in vivo* effects are generally not as strong as that of the uric acid results (DISCUSSION), and such results do not demonstrate any therapeutic efficacy. Moreover, again Applicant has not demonstrated any other genetically modified DH5 cell than the single embodiment discussed throughout this analysis. From this, the Artisan would recognize that these results are simply an invitation for further experimentation, because the Artisan could not reasonably predict an *in vivo* therapeutic effect would occur and the Artisan could not reasonably predict how to genetically modify any DH5 cell to produce any particular efficacious effect. Such prediction is precluded for the reasons given throughout this analysis.

In Prakash (2000) Int. J. Art. Organs, 23(7): 429-35, Applicant demonstrates the lowering of uric acid, both *in vivo* and *in vitro*, similar to the results seen in the present application (ABSTRACT; Article in general). These results are the soul results of Applicant's claimed embodiments that are considered reasonably predictable of efficacious effect.

Hence, for the reasons mentioned throughout, the Artisan could not reasonably predict, absent a specific showing, that the route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected or to reasonably predict whether any particular microencapsulation

material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes, may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected. Moreover, the Artisan, for the above-mentioned reasons, could not reasonably predict that any result obtained *in vitro* would be reasonably predictive of *in vivo* use. Nor could the Artisan reasonably predict which genes to use to genetically engineer the DH5 cells to remove any particular metabolite or any electrolyte *in vivo*, save for the use of urease to remove urea.

Hence, absent a very strong showing by way of example, the claims are not enabled for their fully-claimed scope, as claimed by Applicant.

**The Existence of Working Examples**

Example 1 demonstrates the lowering of the *in vitro* levels of the same metabolites and electrolytes as is reviewed in the section above (guidance and direction). Example 2 specifically demonstrates that rats which were were surgically induced to undergo renal failure could be treated with DH5 cells expressing the same urease gene as the previous DH5 cells in the previous sections, and encapsulated in alginate-polylysine-alginate. Example 3 demonstrates the levels of the other claimed metabolites and electrolytes; however, it is noted that the error bars in the data provided (FIGURES 10-15) demonstrate that for any metabolite examined, other than uric acid, and for any electolyte examined, the data is not statistically significant. Hence, outside a treatment of uric acid levels in a rat, via such microencapsulated DH5 cells, the Artisan could not reasonably predict, absent a specific showing, that the route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which

would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected or to reasonably predict whether any particular microencapsulation material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes, may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected. Moreover, the Artisan, for the above-mentioned reasons, could not reasonably predict that any result obtained *in vitro* would be reasonably predictive of *in vivo* use. Nor could the Artisan reasonably predict which genes to use to genetically engineer the DH5 cells to remove any particular metabolite or any electrolyte *in vivo*, save for the use of urease to remove urea and uric acid.

**The Quantity of Experimentation Needed to Make and/or Use the Invention**

Because of the insufficiency of working the examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to that determine, whether any particular route of administration of such cells would not produce biocompatibility problems, foreign body reaction, or compliment activation which would block any action the microencapsulated cells had in the first place, or even kill the cells before such treatment could be effected or to determine whether any particular microencapsulation material may break, causing release of the DH5 cells, which, depending on their transgene and the levels of metabolites and electrolytes,

may then disturb the floral balance of the intestine, causing dysentery and death before any treatment could be effected or killing the DH5 cells before any treatment could be effected. Moreover, the Artisan, for the above-mentioned reasons, would also need to determine whether any particular *in vitro* would work *in vivo*. Furthermore, the Artisan would need to determine which genes to use to genetically engineer the DH5 cells to remove any particular metabolite or any electrolyte *in vivo*, save for the use of urease to remove urea and uric acid.

**Conclusion**

Because of the large amount of experimentation required to make and/or use the invention within its fully-claimed scope, as claimed by Applicant, such experimentation is considered undue. Therefore, for the reasons given throughout this rejection, the claims are not enabled for their fully-claimed scope.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 rejected under 35 U.S.C. 102(b) as being anticipated by Prakash, et al. (1993) Biomat. Art. Cells Immob. Biotech., 21(5): 629-636.

With regard to Claims 1-5, Prakash teaches *E. coli* DH5 cells (p. 630, fourth paragraph), genetically engineered to express *K. aerogenes* urease (p. 630, third paragraph), and encapsulated in alginate-polylysine-alginate (e.g., pp. 630-631, paragraph bridging).

## CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER